

undue searching burden would be required to examine the full scope of the claims. Such a reason is adequate under MPEP § 818.03(a). Thus, the traversal should be accepted.

Claim 28

Claim 28 was not grouped into any of the Groups in the Office Action making the Election/Restriction requirement. Claim 28 properly belongs to group I, the elected group, drawn to a method of inhibiting the occurrence of advanced endometrium maturation. Applicants respectfully request the consideration of this claim with the elected group.

The Claim Rejections under 35 USC § 112, first paragraph

Claims 1-6, 12-16, 23, 25, 27 and 29 were rejected as allegedly not enabled.

The Examiner appears to challenge the credibility of the applicants' asserted utility as an alleged defect of enabling support.

First and foremost, a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971). "The PTO must have adequate support for its challenge to the credibility of applicant's statements of utility". (The quoted statement was made in the context of enablement, i.e., the how-to-use requirement of the first paragraph of section 112.) See also *In re Bundy*, 209 USPQ 48 (1981). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra*.

The Examiner has provided no support for establishing that one of ordinary skill would doubt the objective truth of the asserted utility, which is enabled by the specification. The Examiner offers no support for such an assertion. The enablement rejections by the Examiner are thus unfounded. The rejection therefore was improper under *In re Marzocchi*, and must be reversed for this reason alone.

Furthermore, in *In re Bundy*, 209 USPQ 48, (1981), the disclosure did not have specific

examples of the compounds claimed, and provided no example of specific use of any of the disclosed compounds, e.g., did not set forth the dosage to achieve the desired response. All that was established at the time of filing was the basic pharmacology for the compounds. The specification stated that the compounds of the invention possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that “what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity.” *Id.*

Applicants satisfy these requirements. Applicants disclose that the 17 α -fluoroalkylated progesterone antagonists inhibit the advancement of endometrium maturation during infertility, i.e., fertility enhancement. See page 1, lines 19 to 22. The specification on page 5, lines 9 to 17, teaches that the antagonists of formula I possess a strong affinity for the gestagen receptor (progesterone receptor) and show minimal gestagen activity of their own. The specification, as noted in the Office Action, provides example 1, which demonstrates the successful use of the 17 α -fluoroalkylated progesterone antagonists in a rabbit model. No reason is given of the PTO to doubt Applicants’ statements that such use extends throughout the claimed scope.

The Office Action alleges that the broadest claim encompasses the administration of a compound of formula I at any time and using any dosage. Applicants however observe that all the claims under consideration have been rejected while many of the claims specify a time, i.e., during the post-ovulatory phase of the endometrial cycle, and also specify a specific dosage, i.e., 0.1-2 mg per subject, etc., for administration.

The broadest claims that recite a compound of formula I are claims 23 and 25. Both of these claims teach that the subject, i.e., human female or non-human female mammal, is undergoing fertility enhancement treatment. Thus, these claims do specify a time, i.e., a time when the subject is undergoing fertility enhancement treatment and inherently specify to a skilled worker when the compound is administered.

Further, the specification also teaches in a preferred mode, more specific timing for the administration of the antagonist as described on page 11, lines 14 to 19.

“According to a preferred mode of operation, the 17 α - fluoralkylated progesterone receptor antagonist is typically administered over a period of 1 to 6 days, preferably 1 to 4 days, and more preferably on day(s) 1-3 after ovulation and/or the removal of oocytes.

Typically, the antigestagen is administered over a period of 1 to 6 days, preferably 1-4 days, and more preferably 1-3 days after ovulation induction with e.g. a chorionic gonadotropin.”

The law does not require an Applicant to specify exact timing or the dose for treatment in a method of treatment claim. Applicants bring the Examiner’s attention to *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), *Cross* hereinafter, wherein the Federal Circuit affirmed a USPTO Board of Patent Interferences decision addressing among other issues as well whether dosage levels even need to be disclosed for a pharmaceutical in order to enable it. The Federal Circuit held that where sufficient credible evidence that one skilled in the art, without the exercise of inventive skill or undue experimentation, could determine dosage levels, disclosure of dosage levels is not necessary for enablement. The court went on to state that knowledge of the pharmacological activities of compounds is beneficial to the medical profession, and requiring an applicant to disclose in vivo dosages in a patent application would delay and frustrate researchers by failing to provide an incentive for early public disclosure of such compounds, thereby failing to further the public interest.

The Manual of Patent Examination and Procedure, is in accord with the *Cross* decision. The MPEP states that it is unnecessary to disclose dosages to satisfy the enablement requirement. See, e.g., MPEP 2164.01(c):

“it is not necessary to specify the dosage ... if it is known in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physical or biological activity would be able to discern an appropriate dosage ... without undue experimentation, this would be sufficient to satisfy 35 U.S.C. § 112, first paragraph.”

The Examiner alleges that it would require undue experimentation to practice the method as claimed. Even if no dosages were disclosed, one of ordinary skill in the art would be able to determine the dosage levels without undue experimentation by following routine activity protocols and the guidance for determining dosages in the specification. However, in this case, applicants even disclose, and also in rejected dependent claims claim specific dosage levels, and give guidance in the specification regarding how to determine the dosage levels. The specification on page 11 lines 20 to page 12, line 8 teaches that:

“Surprisingly, according the invention, it has been found that low doses of a 17α -

fluoralkylated progesterone receptor antagonists are effective in the methods disclosed herein. The 17 α -fluoralkylated progesterone receptor antagonists are preferably administered to a human female subject in a daily dosage amount of up to 10 mg per subject, preferably 0.1 - 2 mg per subject, more preferably 0.1-1 mg per subject, and most preferably 0.1-0.7 mg per subject. For mammals in general, a daily dosage amount is typically 0.01-1 mg/kg, preferably 0.01-0.3 mg/kg, and more preferably 0.01-0.1 mg/kg. The daily dose of antigestagen can be administered as a single dose or as divided dosages throughout the day.

In a preferred embodiment according to the invention, the antigestagen is administered on a single day to a human subject in an amount of 0.1 - 2 mg/per subject, more preferably 0.1-1 mg/per subject, and most preferably 0.1-0.7 mg/per subject or to a mammal in an amount of 0.01-1 mg/kg, preferably 0.01-0.3 mg/kg, and more preferably 0.01-0.1 mg/kg. For example, on day 1, 2, 3, 4, 5 or 6 following ovulation, removal of oocytes, or administration of a chorionic gonadotropin, preferably day 1-3, and more preferably day 2.

For any particular 17 α -fluoralkylated progesterone receptor antagonist, the most appropriate dose can be determined, for example, by evaluation of the potency to induce premature menstruation in advanced luteal phase of the human cycle as described in e.g. Herrmann, W., et al, 1982, *Comptes Rendus* 294:933."

The Office Action alleges in the form of an inquiry that the specification does not teach whether the administration protocol and dosage would be the same for all mammals including humans. Applicants respectfully point the Examiner's attention to the quoted language above, which specifically answers the posed question.

The specification also teaches a variety of methods of administration for therapeutic uses. See specification page 11, lines 5 to 13 that:

"The antigestagens can, for example, be applied locally, topically, enterally or parenterally.

For the preferred oral administration, particularly suitable are tablets, dragees, capsules, pills, suspensions or solutions which can be prepared in a conventional manner with additives and carriers used in pharmacy. For local or topical application, vaginal

pessaries or percutaneous systems such as skin plasters can be used for example. For parenteral application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions or emulsions. Ampules are convenient unit dosages.”

Despite the large amount of direction in the specification that details ranges for doses as well as specific days to administer the compound of the invention, the Office Action alleges that the teaching of the specification is very limited because the specification fails to disclose whether the dosage is effective in inhibiting advanced endometrium in other mammals or human model. However Applicants are not required by law to supply examples of other mammals or humans in order to obtain a patent to the treatment of such. Such showings could only be at issue where doubt of the creditability of a given utility were established, which is not the case here.

In any event, the Examiner’s allegation that the demonstrated rabbit model does not correlate with an *in vivo* therapeutic activity is untenable. This allegation is improper “since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example.” See MPEP § 2164.02. The Examiner provided no support, reasons or evidence, to challenge the truth of the asserted correlation.

The Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir.1995), stated that

“it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans. ... Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were Phase II testing required in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.”

The Federal Circuit in *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 USPQ.2d 1895 (1996),

stated that

“All that is required is the test to be reasonably indicative of the desired pharmacological response. ... There must be a sufficient correlation between the tests and the asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior.”

In *Cross*, supra, the Federal Circuit specifically held that in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo tests results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Applicants in the current case provide a working rabbit model, were one necessary – which is not the case. This is very strong evidence, which would convince those skilled in the art, to a reasonable probability, that the novel compounds will exhibit the asserted pharmacological behavior in non-human mammals as well as in humans.

The Office Action inquires whether the administration of the claimed antagonists at any time during the fertility treatment can inhibit the occurrence of advanced endometrium maturation. Applicants are clear in the specification that the invention is not limited to the administration of the antagonists at specific times during the fertility treatment, but common sense dictates to skilled workers when administration makes no sense, e.g., before ovulation, it is believed. Applicants however teach specific times during fertility treatment that are preferred over others. See quoted material above for example.

The Office Action as part of the reasons for alleging lack of enablement alleges that the specification does not teach whether if the compound is administered before hCG or HMG, would it still inhibit the endometrium maturation after hCG and HMG injection, or whether if the compound is administered long after post-ovulatory phase, would it reverse the endometrium maturation process. The law does not require that an Applicant determine the behavior of claimed compounds in all imaginable, even nonsensible ways. The scope of the claims is enabled.

The Office Action further alleges that for determining the enablement of the claimed method, the parameters in determining the stage of endometrium maturation are critical.

Applicants respectfully disagree. The Office Action even admits that the specification teaches that McPhail-Index, uteroglobin expression and uterine weight are used as parameters to determine the endometrium maturation status and that in the rabbit example the applicants demonstrated advanced endometrium maturation in the rabbits by nearly undetectable uteroglobin expression in endometrial epithelial cells, by increased uterine weight and by increased McPhail-Index as disclosed on page 16, lines 7-11 and table 1. Applicants thus not only disclosed the parameters in determining the stage of endometrium maturation, but even demonstrated it in an example. Nothing more is required of applicants.

The Office Action alleges that the results in Table 1 for higher concentrations are confusing, thus making the claimed treatment methods unpredictable. Applicants respectfully submit that there is nothing confusing about the results. The specification teaches in the context of the rabbit model that "higher doses of progesterone receptor antagonist, 1 mg/kg (group 4) and 10 mg/kg (group 5), apparently counteracted the advancement of endometrium maturation associated with ovarian hyperstimulation and also delayed the timing of maturation beyond that observed in animals which were not subject to hyperovarian stimulation." See page 16, lines 17 to 21. These are the results and the conclusions drawn therefrom. There is no confusion. Applicants on page 11, lines 20-22, in language already quoted above, teach that surprisingly, low doses of the antagonists are effective in the methods. Applicants then go on to teach preferred doses.

The Office Action alleges that the teachings of the specification are not commensurate in scope with the present claims. Applicants are not even required to disclose dosages in order to enable the presently claimed subject matter. See discussion above. Applicants are thus not required to limit the broadest claims to the preferred dosages disclosed.

Reconsideration of all the rejections is respectfully requested.

The Claim Rejections under 35 USC § 112, second paragraph

Claims 1-6, 12-16, 23, 25, 27 and 29 were rejected as allegedly indefinite for not including the parameters by which one would determine whether advanced endometrium maturation is inhibited.

Applicants respectfully disagree. Applicants are claiming a method of inhibiting advanced

endometrium maturation, and are not claiming a method for inhibiting and determining the result after the method was practiced. Determining whether endometrium maturation inhibition indeed occurred is not an essential step of inhibiting advanced endometrium maturation. The inhibition of advanced endometrium maturation occurs regardless of whether one determines if it occurred. Thus, determining whether advanced endometrium maturation is inhibited is not an essential step of the claimed invention. Thus, the claims are not indefinite. Reconsideration is requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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